SYNTHETIC STUDIES ON ERIOLANIN: 1,2-CARBONYL TRANSPOSITIONS OF CIS-BICYCLO[4.2.0]OCTANONE VIA ENOL THIOETHER FORMATION

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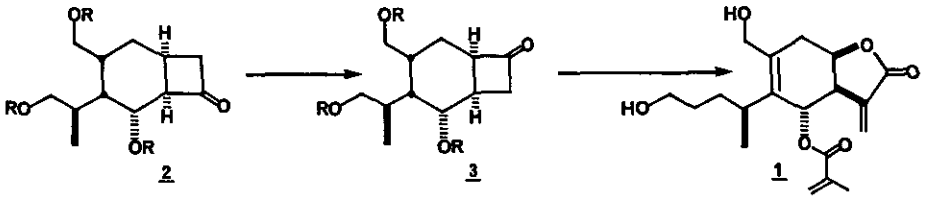
Abstract — 1,2-Carbonyl transposition of cis-fused cyclobutanone is demonstrated by means of two procedures(method A and method B). This relatively short sequence(method B) provides a new and convenient method for conversion of carbonyl group in the entitled ring system.

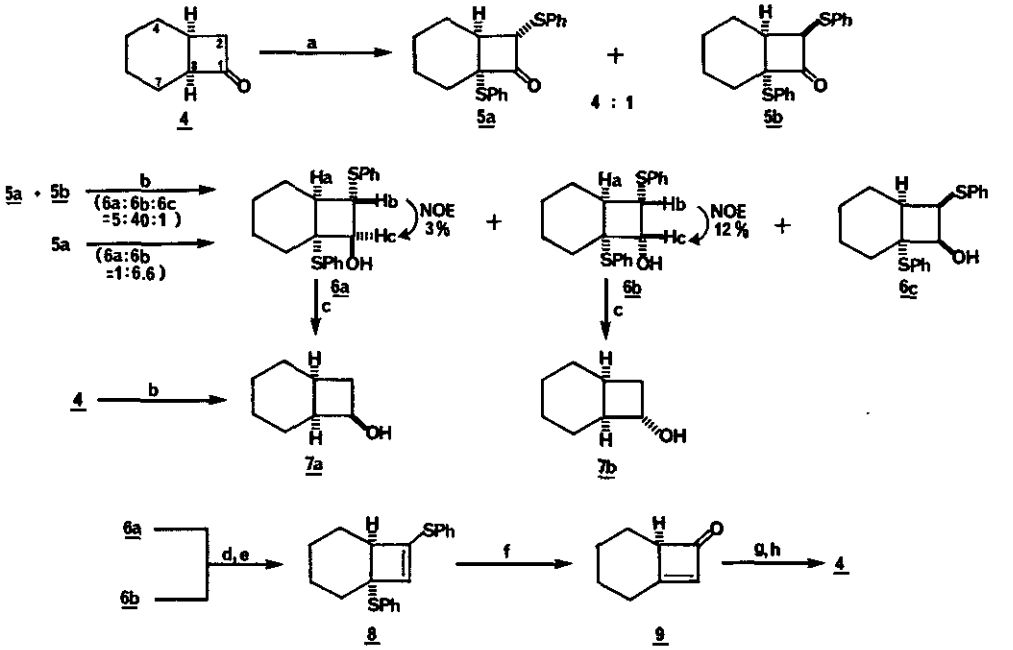
Dichlorocyclobutanones, readily available by dichloroketene cycloadditions to olefins[1] are extremely useful intermediates in organic synthesis.[2] In a continuation of our work directed toward the synthesis of an antitumor sesquiterpene, eriolanin 1[3], we required a concise and general method for 1,2-carbonyl transposition [2 → 3] in cis-bicyclo[4.2.0]octanone system.
While previous works on various aspects of carbonyl transposition have been reported, methods to transpose the carbonyl group of ketones are lacking[4] in the entitled ring fusion.
We now report the two different methods A and B on 1,2-carbonyl transposition, which provided enol thioethers 8 or 14 respectively as intermediates for cyclobutanones.



Treatment of 4 with lithium bis(trimethylsilyl)amide in tetrahydrofuran(THF) at -78°C to 0°C for 1.5 h followed by addition of diphenyldisulfide(2.5 equiv)[5] in hexamethylphosphoric triamide(HMPA) at 0°C for 14 h gave bis(phenylthio)-cyclobutanones 5a and 5b in a 4:1 ratio in 90% yield.

It is difficult to control the regioselectivity for monosulfenylation of 4 at C-2 position via deprotonation with an amide base. Enolization usually occurs at C-8 to yield the corresponding cyclobutanone enolate.[2a,6] Reduction of 5a[7] with sodium borohydride afforded smoothly a 1:6.6 mixture of 6a[7][^{1}H NMR($CDCl_3$)δ 3.34(dd, J_{bc}=7.8 and J_{ab}=10.0 Hz, $1H_b$),3.93(d, J_{bc}=7.8Hz, $1H_c$)] and 6b[7][^{1}H NMR($CDCl_3$)δ 3.88(dd, J_{bc}=4.8 and J_{ab}=10.0Hz,$1H_b$),4.02(d, J_{bc}=4.8Hz,$1H_c$)] in quantitative yield, of which the stereochemistry was determined from J values of ^{1}H NMR, the observation of NOE and chemical transformations as shown in Scheme 1. A similar reduction of 4:1 mixtures 5a and 5b afforded 6a, 6b, and 6c in a raitio of 5:40:1 in 91% yield, of which compound 6c arose from 5b. Desulfurization of 6a and 6b with Raney Ni(W-2) in ethanol led to their cyclobutanols 7a and 7b respectively, while 7a was available from the reduction of cyclobutanone 4.[8] Hence, the reduction products were found to possess the stereochemistry indicated. Treatment of 6a and 6b with methanesulfonyl chloride in pyridine and subsequent elimination of the resulting methanesulfonates with potassium tert-butoxide in dimethyl sufoxide at room temperature produced effectively the same enol thioether 8[7][mp 47°C; ^{1}H NMR($CDCl_3$)δ 5.93(s,1H);Mass m/z 324(M^+)] in good yields. Hydrolysis of 8 with mercuric chloride in aqueous acetonitrile at room temperature[5] gave spontaneously cyclobutenone 9[7] in 45% isolated yield.

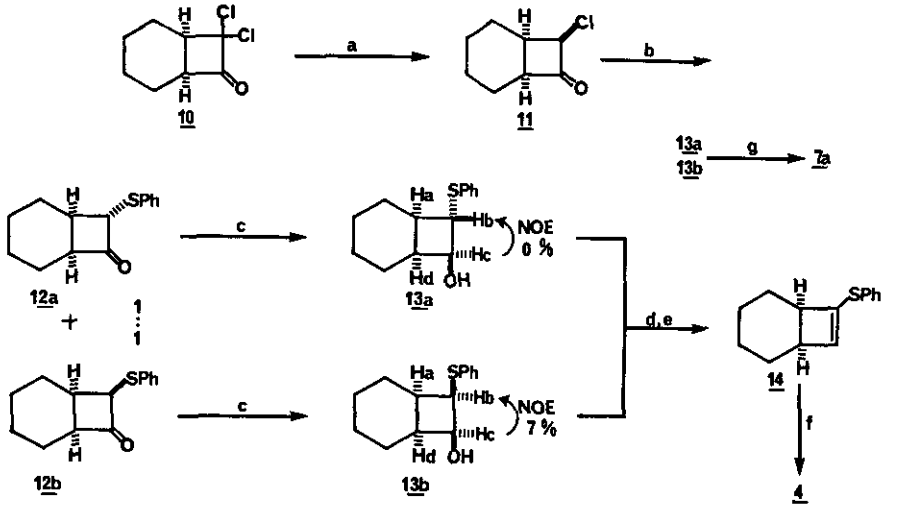
Scheme 1 (method A)



a $LiN(TMS)_2$(3 equiv)/THF/-78°C→0°C,then PhSSPh(2.5 equiv)/HMPA/0°C,90% ; b $NaBH_4$/MeOH,99% from 5a, 90% from 5b ; c Raney Ni(W-2)/EtOH/rt ; d MsCl/pyr. /rt ; e t-BuOK/DMSO/rt,76% from 6a, 84% from 6b ; f $HgCl_2/CH_3CN$-H_2O(3:1)/rt, 45% ; g H_2/Pt/AcOEt ; h PCC/Molecular Sieves 3A/CH_2Cl_2,33% from 9

Catalytic hydrogenation of double bond in 9 with platinum under a hydrogen atmosphere gave rise to the overreduced cyclobutanol, which was immediately oxidized to cyclobutanone 4 with pyridinium chlorochromate in dichloromethane in 33% overall yield.

Scheme 2 (method B)

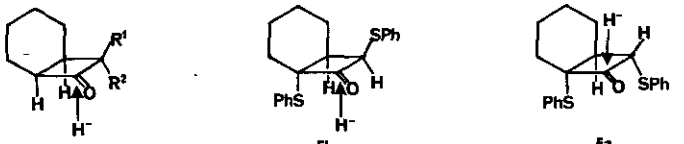


a Zn/NH_4Cl-MeOH/0°C,30min,61% from cyclohexene ; b PhSNa/MeOH/0°C→rt,86% ; c $NaBH_4$/MeOH,80% from 12a, 90% from 12b ; d MsCl/pyr./rt ; e t-BuOK/DMSO/rt, 87% from 13a, 100% from 13b ; f $HgCl_2/CH_3CN$-H_2O(3:1)/50°C,62% ; g Raney Ni(W-2)

To improve the later stage in method A, we next turned our attention to the following method B which provided a more convenient and easy operation rather than method A. Dichlorocyclobutanone 10 was carefully reduced with zinc in methanolic ammonium chloride[9] at 0°C for 30 min to afford monochlorocyclobutanone 11[^{1}H NMR($CDCl_3$)δ 4.95(dd, J=2.2 and 8.8 Hz, 1H)] as the sole product in 61% yield from cyclohexene. When 11 was allowed to react with sodium thiophenolate in methanol, an 86% yield of a 1:1 mixture of diastereoisomers 12a[7][^{1}H NMR ($CDCl_3$)δ 4.16(dd, J=2.2 and 5.4 Hz, 1H)] and 12b[7][^{1}H NMR($CDCl_3$)δ 4.65(dd, J=2.2 and 8.5Hz, 1H)] was obtained. These diastereoisomers were easily separated by chromatography on silica gel. Reduction of 12a and 12b with sodium borohydride gave their cyclobutanols 13a[7][^{1}H NMR($CDCl_3$)δ 3.54(dd, J_{bc}=7.6 and J_{ab}=10.0Hz, ,$1H_b$),3.99(t, J_{bc}=J_{cd}=7.6Hz,$1H_c$)] and 13b[7][^{1}H NMR($CDCl_3$)δ 4.16(ddd,J_{bd}=2.2,J_{bc}= 6.1, and J_{ab}=8.3Hz,$1H_b$),4.50(dt, J_{ac}=2.0 and J_{bc}=J_{cd}=6.1 Hz,$1H_c$)] respectively in good yields. Stereochemistry of 13a and 13b obtained in this way was established in the similar manner mentioned above and results were indicated in Scheme 2. The enol thioether 14[7][H NMR($CDCl_3$)δ 5.90(d,J=0.7 Hz,1H); Mass m/z 216(M^+)] was obtained both from 13a and 13b in two steps (I) MsCl/pyridine (II) t-BuOK/DMSO.

Finally, hydrolysis of the resulting enol thioether 14 with mercuric chloride at 50°C produced the desired cyclobutanone 4 in 62% yield. All reaction mixtures produced from either method A or B are not required their separations since they yield the same enol thioethers 8 or 14. This method should provide ready access to 1,2-carbonyl transposition of cis-bicyclo[4.2.0]octanone derivatives. Stereochemistry during reduction of cyclobutanones 5a, 5b, 12a, and 12b with sodium borohydride resulted in steric control as indicated in Scheme 3. We are currently exploiting this methodology in our approaches to the synthesis of eriolanin 1.

Scheme 3



12a R^1=H,R^2=SPh 5b 5a

12b R^1=SPh,R^2=H

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